

MAR | 6 1999

**FREEDOM OF INFORMATION SUMMARY  
FOR  
SYNOVEX<sup>®</sup> Plus<sup>™</sup> (Estradiol Benzoate and Trenbolone Acetate)**

**1. GENERAL INFORMATION**

NADA Number: 141-043

Sponsor: Fort Dodge Animal Health  
Div. of American Home Products Corp.  
800 Fifth St. NW.  
Fort Dodge, IA 50501

Generic Name: Trenbolone Acetate and Estradiol Benzoate

Trade Name: Synovex<sup>®</sup> Plus

Marketing Status: Over-the-counter (OTC)

Effect of Supplement: This supplement provides for the implantation of Synovex<sup>®</sup> Plus in steers fed in confinement for slaughter for increased rate of weight gain.

**2. INDICATIONS FOR USE**

For increased rate of weight gain and improved feed efficiency in steers and for increased rate of weight gain in heifers fed in confinement for slaughter.

**3. DOSAGE FORM(S), ROUTE OF ADMINISTRATION, AND RECOMMENDED DOSAGE**

The dosage form is implantation. The route of administration is subcutaneous implantation on the posterior aspect of the middle one-third of the ear by means of an implant gun. The recommended dosage is one implant containing 200 mg trenbolone acetate (TBA) and 28 mg estradiol benzoate (EB). The implant consists of eight pellets with each pellet containing 25 mg TBA and 3.5 mg EB. Each implant is contained in one division of a ten dose cartridge. The cartridge is designed to be used with a Synovex implanting device.

**4. EFFECTIVENESS**

The effectiveness requirement for this supplemental new animal drug application for Synovex Plus in steers, with the indications for use and dosage as given in Sections 2 and 3 above, is met by utilizing the existing database in NADA 141-043 and conducting the additional adequate and well-controlled studies included in this supplemental application.

NADA 141-043

3  
FOIS-2

### **Pivotal Studies:**

A dose titration study was conducted at three sites using a uniform protocol such that the results could be pooled and summarized. The three sites were in major beef producing areas of the United States using management systems and diets typical of commercial feedlots.

#### **Name and Address of Investigators:**

James J. Sheldon, D.V.M., Ph.D.  
Sheldon Agri-business  
Casa Grande, AZ  
Study Location: El Centro, CA

Rodney L. Preston, Ph.D.  
Texas Tech University  
Department of Animal Science  
Lubbock, TX  
Study Location: New Deal, TX

Alvin Edwards, D. V. M., Ph.D.  
Kansas State University  
College of Veterinary Medicine  
Manhattan, KS  
Study Location: Lamar, CO

The purpose of the studies was to evaluate the dose response for TBA and EB on average daily gain (ADG) of steers fed in confinement for slaughter. The test animals were cross-bred animals of Brahman, English, and Exotic breeds. For each study, 360 steers were randomized on the basis of weight into 5 blocks of 9 pens with 8 animals per pen, and administered one of the following treatments: 0/0, 0/300, 60/0, 14/100, 28/200, and 42/300 (mg EB/mg TBA). The steers weighed approximately 600 pounds when the studies were initiated. The duration of the studies ranged between 132 to 183 days.

Each steer was administered EB/TBA via subcutaneous implantation of the backside of the mid-ear. The control steers were not implanted. The steers were implanted once at the initiation of the study.

ADG data for the steers are summarized in Table 1 for each of the three dose titration studies.

A randomized complete block design was used for all studies and the data were pooled by analysis of variance to determine the significance of the effect of the EB/TBA implant on ADG. There was a significant ( $P < .05$ ) dose effect on ADG with the response plateauing at a dose of 14mgEB/100 mg TBA. The 28 mg EB/200 mg TBA dose was shown to be

significantly ( $P < .05$ ) better than controls, 300 mg TBA alone, and 60 mg EB alone. These data are sufficient to support the claims and dosage as provided in Sections 2 and 3.

TABLE 1. SUMMARY FROM THREE DOSE TITRATION STUDIES COMPARING THE EFFECT OF VARIOUS LEVELS OF TRENBOLONE ACETATE AND ESTRADIOL BENZOATE ON AVERAGE DAILY GATN IN FEEDLOT STEERS

EB/TBA (mg)	Location			
	Texas	Colorado	California	Pooled Average
0/0	2.26	3.41	3.10	2.93
0/300	2.53	3.66	2.96	3.06
60/0	2.65	3.66	3.36	3.23
14/100	2.89	3.87	3.38	3.38
28/200	2.82	3.86	3.59	3.43
42/300	2.87	4.08	3.59	3.52

The effects of treatment on yield grade, quality grade, marbling score, and liver abscess incidence were evaluated at slaughter. A decrease in marbling scores was observed. No effect of treatment was seen in yield grade or the incidence of liver abscesses. Because of the observed decrease in marbling scores, the following statement is required on the label: Studies have demonstrated that the administration of Synovex Plus can result in decreased marbling scores when compared to non-implanted steers.

## 5. TARGET ANIMAL SAFETY

Target animal safety is established by data in the parent application. Therefore, no further studies were required.

## 6. HUMAN SAFETY

Human safety is established by data in the parent application. Therefore, no further studies were required.

## 7. AGENCY CONCLUSIONS

Adequate data demonstrates the safe and effective use of Synovex<sup>®</sup> Plus for increased rate of weight gain when administered to steers fed in confinement for slaughter.

Under the Center's supplemental approval policy (21 CFR 514.106(b)(2)), this is a Category II change providing for the implantation of Synovex<sup>®</sup> Plus in steers fed in confinement for slaughter. The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

## **8. LABELING**

Three (3) pages of labeling are attached as follows:

1. Implant folding carton label
2. Implant fold-out labels of outer folding carton
3. Foil pouch label

IMPLANTS FOR STEERS AND HEIFERS FED IN CONFINEMENT FOR SLAUGHTER

# SYNOVEX<sup>®</sup> PLUS<sup>™</sup>

(trenbolone acetate and estradiol benzoate)

NADA 141-043  
Approved by FDA

NDC 0856-3904-10

FOR ANIMAL USE ONLY.  
NOT FOR USE IN HUMANS.

#### INDICATIONS FOR USE:

Synovex Plus is recommended for increased rate of weight gain and improved feed efficiency in steers and for increased rate of weight gain in heifers fed in confinement for slaughter.

NET CONTENTS: One pouch contains ten 10-dose cartridges (100 implants).

Manufactured By A  
Non-Sterilizing Process

Keep this and all drugs out of the reach of children.

Restricted Drug (California)—  
Use Only As Directed.

IMPORTANT: Read ALL  
sides of carton

FORT DODGE<sup>®</sup>

NET CONTENTS: 10 CARTRIDGES  
Each Cartridge Contains 10 Rows of 8 Pellets

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# SYNOVEX<sup>®</sup> PLUS<sup>™</sup>

(trenbolone acetate and estradiol benzoate)

Synovex Plus (trenbolone acetate and estradiol benzoate) is a growth promoting implant containing 200 mg of trenbolone acetate and 28 mg of estradiol benzoate. Each implant consists of 8 pellets. Ten implants are provided in each cartridge.

NOTE: Studies have demonstrated that the administration of Synovex Plus can result in decreased marketing scores when compared to non-implanted steers and heifers.

DOSAGE: One implant (eight pellets), containing 200 mg of trenbolone acetate and 28 mg of estradiol benzoate, is administered to each steer or heifer by subcutaneous implantation in the middle one-third of the ear.

The ten-dose cartridge of Synovex Plus is designed to be used exclusively with a Syrovex implanting device.

WARNING: Not for dairy or beef replacement heifers. Implant pellets in ear only. Any other location is a violation of Federal law. Do not attempt salvage of implanted site for human or animal food.

FOR ANIMAL USE ONLY.  
NOT FOR USE IN HUMANS.

FORT DODGE<sup>®</sup>

NET CONTENTS: 10 CARTRIDGES  
Each Cartridge Contains 10 Rows of 8 Pellets

CAUTION: Bulling, vaginal and rectal prolapse, udder development, ventral edema and elevated tailheads have occasionally been reported in heifers administered Synovex Plus implants.

DIRECTIONS: Implant complete contents of one cartridge cell per steer or heifer. Approved implantation technique is fully described in the fold-out carton section.

NOTE: Never sacrifice careful, clean technique for speed of implantation.

STORAGE: Store unopened product at room temperature. Avoid excessive heat and humidity. Use product before the expiration date on the label.

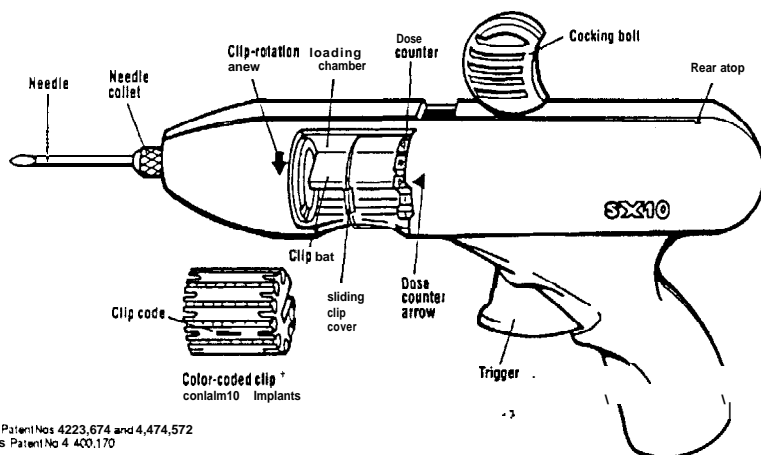
Once the pouch is opened, unused product may be stored in the end-folded pouch (away from light) for up to six months under refrigerated conditions (2-8 °C/36-47°F) or at room temperature (15-30°C/59-86°F) for up to one month.

FORT DODGE<sup>®</sup>

Fort Dodge Animal Health  
Fort Dodge, Iowa 50501 USA

Open here for implanting directions

# SYNOVEX® SX10® Gun\*



U.S. Patent Nos. 4,223,674 and 4,474,572  
U.S. Patent No. 4,400,170

## HOW TO IMPLANT

### SYNOVEX<sup>PLUS</sup>™

#### PELLETS

For Use With Any Synovex Gun.

Study the following instructions carefully, then proceed step by step, until the technique becomes routine. Many heads can be implanted per hour by an experienced team, one member of which should be assigned to do nothing but the implantation. Care should be taken to insure the hands of the person administering the implant are clean and only sanitary instruments are used.

## SYNOVEX<sup>PLUS</sup>™ Implants

Synovex Plus is recommended for steers and heifers fed in confinement for slaughter. When properly administered, Synovex Plus implants increase rate of "weight gain and improve feed efficiency in steers and increase rate of weight gain in heifers.

#### STORAGE

Store unopened product at room temperature. Avoid excessive heat and humidity.

Use product before the expiration date, printed on the label.

Once the pouch is opened, unused children product may be stored in the end-folded Restricted Drug (California)—pouch (away from light) for up to six months under refrigerated conditions (2–8°C/36–47°F) or at room temperature (15–30°C/59–86°F) for up to one month.

**WARNING**  
Not for dairy or beef replacement heifers. Implants are for use only in ear only. Any other location is a violation of Federal law. Do not attempt salvage of implanted site for human or animal use.

Keep this and all drugs out of the reach of children.

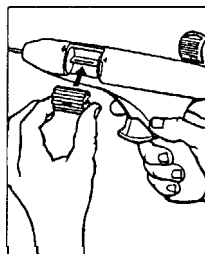


Exp. Date

Lot



## STEP 1 Loading The SX10 Gun



Load the SX10 gun following the directions outlined in the instruction manual accompanying each SX10 gun.

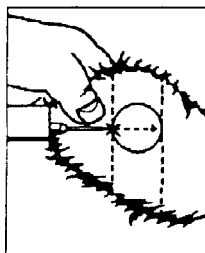
## STEP 2 Restraint



The animal must be confined in a restraint mechanism (squeeze chute or head gate). The implant site on the back of the ear should be prepared by scrubbing with a generous-sized piece of cotton that has been soaked in a germicidal solution.

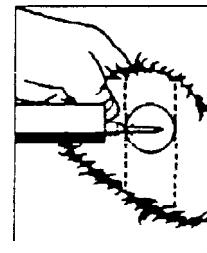
**Note:** If implanting horned cattle, greater safety is provided when the head is controlled by the use of a bull lead (nose tongs).

## STEP 3 Implant Site



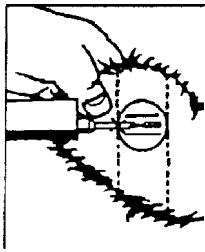
Divide the ear into three imaginary sections as illustrated. The implanted pellets should be deposited in the center one-third of the ear as shown. To accomplish this, the SX10 gun needle should be inserted in the outer one-third of the ear as indicated by the "X" in the illustration. Implanting too close to the head may cause abnormal sexual behavior. Care should be taken to avoid severing the major arteries of the ear.

## STEP 4 Insert Needle



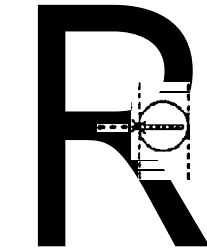
Just before grasping the ear with one hand, release the safety by striking the bun of the gun. Holding the SX10 gun firmly with the other hand, penetrate the skin at the point shown by the "X". Thrust the needle under the skin taking care not to penetrate the cartilage. Ease the SX10 gun forward (toward the base of the ear) until the full needle length is beneath the skin.

## STEP 5 Pellet Implantation



When the needle is completely inserted, activate the instrument by squeezing the trigger completely. Do not withdraw the needle, but allow the automatic needle retractor to release the pellets. This will allow the pellets to be deposited in a straight line in the path of the retracted needle.

## STEP 6 Inspection



Check the implant site. If properly administered, the implants should lie in a straight line under the skin.

Disinfect the SX10 gun needle in a germicidal solution and race the instrument by rotating the cocking grip left, pull back, rotate right, then push all the way forward. You are now ready to implant the next animal.



IMPLANTS FOR STEERS AND HEIFERS FED IN CONFINEMENT FOR SLAUGHTER

# SYNOVEX<sup>®</sup> PLUS<sup>™</sup>

(trenbolone acetate and estradiol benzoate)

NADA 141-042

Approved by FDA

NDC 0856-9984-16

Synovex Plus (trenbolone acetate and estradiol benzoate) is a growth promoting implant containing 200 mg of trenbolone acetate and 28 mg of estradiol benzoate. Each implant consists of 8 pellets. Ten implants are provided in each cartridge.

**INDICATIONS FOR USE:** Synovex Plus is recommended for increased rate of weight gain and improved feed efficiency in steers and for increased rate of weight gain in heifers fed in confinement for slaughter.

**NOTE:** Studies have demonstrated that the administration of Synovex Plus to heifers results in increased carcass weight and improved feed efficiency in steers and heifers.

**DOSEAGE:** One implant (eight pellets) containing 200 mg of trenbolone acetate and 28 mg of estradiol benzoate is administered to each steer or heifer by subcutaneous implantation in the middle of the neck.

The 10-dose cartridge of Synovex Plus is designed to be used exclusively with a Synovex Implanting Device.

**WARNING:** Not for use in or on heat replacement heifers. Implant pellets in ear only. Any other location is a violation of Federal law. Do not attempt salvage of implanted site for human or animal food.

**FOR ANIMAL USE ONLY - NOT FOR USE IN HUMANS**

**CAUTION:** Bulling, vaginal and facial prolapse, horder development, ventral edema and elevated tailheads have occasionally been reported in heifers administered Synovex Plus implants.

**DIRECTIONS:** Implant complete contents of one cartridge on either side of heifer. Approved implantation technique is fully described in the fold-out instruction section.

**NOTE:** Never sacrifice careful clean technique for speed of implantation.

**STORAGE:** Store unopened product at room temperature. Avoid excessive heat and humidity. Use product before the expiration date on the label.

Once the pouch is opened, unused product may be stored in a resealable plastic bag away from light for up to six months under refrigerated conditions (2-8°C or 32-45°F) or at room temperature (15-30°C or 59-85°F) for up to one month.

Manufactured by A Non-Sterilizing Process. Keep this and all containers of the product children Resistant. Drug (Galkman) Use Only As Directed.

Sealed pouches for animal use only.

Fort Dodge Animal Health  
Fort Dodge, Iowa 50501 USA

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**NET CONTENTS:** One pouch contains ten 10-dose cartridges (100 implants)